PREFACE

The thesis work delineates the rational design and successful syntheses of platinum(II) complexes for achieving light promoted dual action anticancer properties. The research work focuses on the syntheses, elaborate characterization including crystallization and mechanistic aspects of photodegradation processes. Theoretical studies were done to elucidate the properties of the excited states. The interaction of active Pt(II) species with DNA is also explored. The cellular studies include evaluation of the photo-induced cytotoxicities, mode of cell death, nature of reactive oxygen species (ROS), quantification of cellular Pt content and cellular and sub-cellular localization of the complexes.

Chapter I provides an overview of the hallmarks of cancer and the current anticancer treatment modalities. It outlines the evolution of platinum based chemotherapeutic drugs, their mechanism of action and associated disadvantages. It also depicts the resurgence of metal complexes as photosensitizers for photoactivated chemotherapy, a selective tripartite strategy which permits light induced tumor destruction. Detailed literature reports of potential transition metal complexes showing light induced generation of ROS and controlled delivery of multiple drugs in tumor microenvironment are presented. The key challenges are the delivery and controlled activation of the clinically approved platinum(II) drugs. These prime objectives of the present investigation are depicted as a concluding segment of this introductory chapter.

Chapter II includes the syntheses, characterization, evaluation of visible light induced cytotoxicity and interaction with DNA of novel ferrocenyl terpyridine appended platinum(II) complexes. Detailed mechanistic investigations revealed the important role of ferrocene in light triggered generation of reactive oxygen species. The effect of extensive conjugation on the photophysical properties of the

complexes were also rationalized from theoretical calculations. The alteration in DNA binding affinities of the complexes on incorporation of a ferrocene unit in the platinum(II)terpyridines is also reflected. The work is the first report of the remarkable photocytotoxicity of platinum(II) complexes in visible light with nominal dark toxicity.

Chapter III deals with novel ferrocenyl terpyridyl platinum(II) complexes having tumor targeting biotinylated acetylides which were synthesized for achieving selective photocytotoxicity only in cancer cells. An interesting observation was the red light promoted release of biotinylated acetylide ligands from platinum centre thereby generating mono-functional Pt(II) species. The possible covalent interactions of these platinum(II) species with DNA were also explored. These biotin complexes exhibit preferential cellular uptake in BT474 breast cancer cells over HBL-100 breast normal cells resulting in targeted photocytotoxicity in visible light.

Chapter IV rationalizes design, syntheses and extensive characterization of 2-(phenylazo)pyridine based platinum(II) catecholates containing photosensitizers. The O^O donor ligand was chosen to release the more cytotoxic bi-functional platinum(II) species based on the prior knowledge of the labile Pt-O bonds. Interestingly, we observed glutathione triggered release of the catecholates imparting dual action anticancer properties to the molecules. Detailed mechanistic aspects indicated a possible reduction of the metal coordinated azo bond by cellular glutathione. The excellent photocytotoxicity in HaCaT and MCF-7 cells, cellular ROS generation and apoptosis, cellular Pt content and localization of these complexes are discussed.

Chapter V addresses the advantages of navigating the platinum(II) complexes to mitochondrial DNA instead of genomic DNA. BODIPY appended platinum(II) catecholates were synthesized and the BODIPY core was modified to fine-tune the photophysical properties. The visible light induced growth inhibitory

effects of the complexes and the mechanism of cell death in light exposed cells are explored. The novelty of this work is the mitochondria targeted remarkable photocytotoxicity as well as cellular imaging properties of the complexes making them ideal candidates for developing platinum based theranostic agents.

Chapter VI presents the syntheses, characterization of unprecedented platinum(II) complexes of curcumin for dual action DNA crosslinking and photochemotherapeutic activities. The important feature of these Pt(II) prodrugs is the photorelease of curcumin from Pt(II) centre which results in controlled delivery of two potential anticancer agents. The visible light induced cytotoxicities of the complexes in HaCaT, BT474, T47D, Hep3B and HPL1D cells, their effect on the various cellular events, the interaction of the complexes with DNA and their cellular distribution in light and dark are explored.

The appropriate references are provided at the end of each chapter and allocated as superscripts in the main text. The synthesized complexes are denoted by bold-faced numbers. Crystallography data of the complexes that are structurally characterized by single crystal X-ray crystallography are given in CIF format in the enclosed CD (Appendix-I). Due acknowledgements are provided for mentioned literature reports. Any omission is purely unintentional and is deeply regretted.

INDEX WORDS: Platinum(II) complexes • Crystal structure • Visible light induced cytotoxicity • Cellular imaging • Photochemotherapeutic agents • DNA crosslink.

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